REMARKS

Favorable reconsideration is respectfully requested.

The claims are 1 to 6 and 8 to 25.

Applicants acknowledge with appreciation the indication that claims 3-5, 12 and 17-22 would be allowable if rewritten in independent form. However, for reasons below, it will be seen that all claims are now in condition for allowance.

Claims 1and 8 are currently amended.

The amendment to claim 1 is supported on pages 8-11 of the specification.

The amendment to claim 8 is self-explanatory.

No new matter is added.

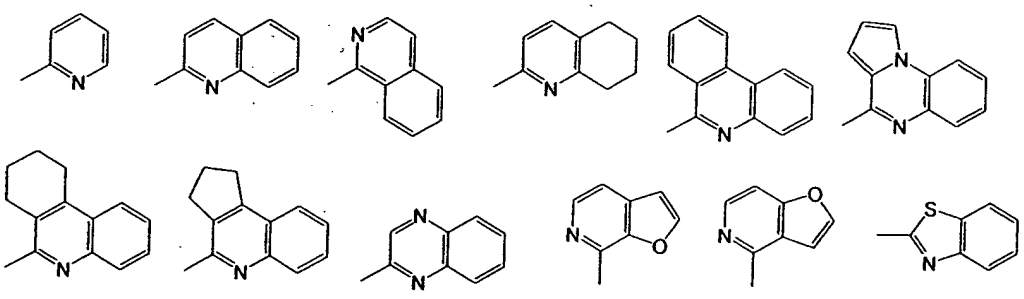
The above amendment is responsive to points set forth in the Official Action, and places the claims into better condition for allowance. Accordingly, entry under the provisions of 37 CFR § 1.116 is fully warranted and respectfully requested.

Claim Rejections - 35 U.S.C. § 112

Claims 1 and 17 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Applicants respectfully traverse.

The Examiner maintains his view that the Ar group defined in Claim 1 is indefinite and ambiguous. The Examiner asserts in the Official Action that if Applicants replace the above-mentioned Ar group with the twelve structures given at page 15 in the last reply:



the Examiner would withdraw the rejection.

The above-mentioned twelve moieties are, however, exactly the same as those in compounds which are disclosed in Examples of the present specification.

The present invention is based on the discovery of compounds which have an effect on IBS by binding both to the 5-HT_{1A} receptor and to the 5-HT_3 receptor.

Most compounds which have binding activity to intracerebral amine receptors such as 5-HT_{1A} have aryl piperazine in their moiety structure, and have a hydrophobic group (R in the following Fig. 1) via several atoms from said aryl piperazine:

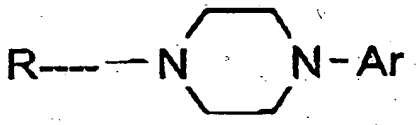


Fig. 1

On the other hand, in most compounds which have binding activity to the 5-HT_3 receptor, a bulky amine (left side of the following Fig. 2) is combined with monocyclic, bicyclic or tricyclic nitrogen-containing heterocycle (right side of the same):

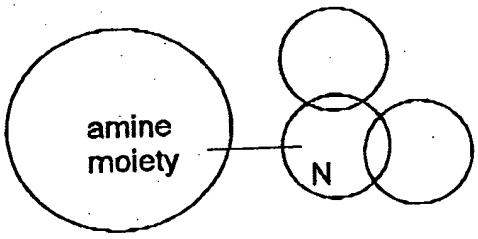


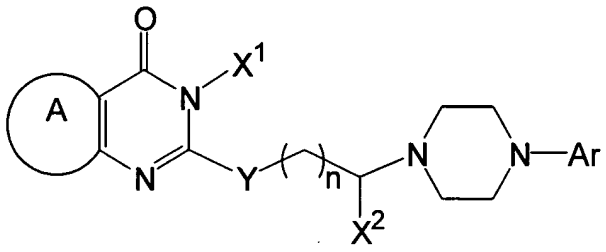
Fig. 2

Seeking compounds which might bind both to 5-HT_{1A} receptor and to 5-HT_3 receptor, the inventors of the present invention assumed that:

1) the amine moiety in a compound (Fig. 2) having activity to bind to 5-HT_3 receptor corresponds to aryl piperazine structure in compound (Fig. 1) having activity to bind to 5-HT_{1A} receptor, and

2) the nitrogen-containing heterocycle in Fig. 2 corresponds to Ar in Fig. 1.

Thus, the present inventors considered that, by replacing R in various ways while maintaining the piperazine-Ar structure in Fig. 1, they would be able to obtain a compound which would show activity to bind to the 5-HT_3 receptor while retaining activity to bind to the 5-HT_{1A} receptor. Taking various species of hydrophobic group (R) in Fig. 1, the present inventors discovered the condensed pyrimidine structure, like quinazoline, as a hydrophobic group (R) which has affinity with the 5-HT_3 receptors without losing affinity to 5-HT_{1A} receptor. This gives the compounds of the present invention of the following general formula:



At the time the present application was filed, there had been known no compounds of the type of Fig. 1 that bound both to the 5-HT_{1A} receptor and to the 5-HT_3 receptor.

In the above formula, it is the condensed pyrimidine moiety and the piperazine moiety which is at a suitable distance from the former, that contribute to 5-HT_{1A} receptor binding activity and 5-HT_3 receptor binding activity. Ar is only a moiety which is positioned at the terminal (Ar is nevertheless important, although at the terminal).

In response to the pending Final Rejection, Applicants define Ar to be the concrete moieties which are mentioned in the present specification at pages 8-11. These moieties are those in compounds which are mentioned in Examples of the present application and the like, whose scope is well defined.

The present amendment therefore overcomes the Examiner's rejection under 35 U.S.C. § 112, second paragraph.

Claims Rejections- 35 U.S.C. § 103

Claims 1-2, 7, 9-11, 13 and 15 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over Matsuoka et al. (CA 2431406).

Claims 1, 6, 8-11, 13-15 and 23-25 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Modica et al. (*High Potent and Selective Arylpiperazine Derivatives as Ligands for the 5-HT1A Receptor*, Bioorganic & Medicinal Chemistry Letters, 10(10), 1089-1092 (2000)).

Claims 1, 6-7, 9-11, 13-16 and 23-25 stand rejected under 103(a) as being unpatentable over Guccione et al. (*3D-QSAR Using "Multiconformer" Alignment: The Use of HASL in the Analysis of 5-HT1A Thienopyrimidinone Ligands*, Journal of Computer-Aided Molecular Design, 14(7), 647-657 (2000)).

Applicants respectfully traverse each of these rejections.

1. *Matsuoka et al.*

The present invention, as described above, is directed to compounds which bond both to the 5-HT_{1A} receptor and to the 5-HT_3 receptor.

The Examiner cites Matsuoka et al. and states: "X^1 can still be lower alkyl and hydrogen and methyl are homologs of one another." The Examiner also cites *In re Wood*, 199 USPQ 137 (CCPA 1978) and *In re Lohr*, 137 USPQ 548, 549 (CCPA 1963) and states: "the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity."

Matsuoka et al., however, relates to compounds which have poly(adenosine 5-diphaspho-ribose) polymerase (PARP) inhibitory activity. PARP is an enzyme which plays a role of repairing DNA when cellular DNA is damaged. When, however, DNA cerebral neurons are damaged by radicals which are generated in large amount in the brain at the time of cerebral

lesion, if PARP is abnormally activated, the substrate NAD^+ is consumed on a large scale, and the ATP synthesizing system is stopped. Thus, intracellular energy is exhausted, resulting in the death of neurons. Hence, it has been tried to protect cerebral neurons by administering agents which inhibit PARP at the time of cerebral lesion.

As mentioned above, Matsuoka et al. concerns the central nervous system, and is quite different in technology from the present invention which concerns digestive organs systems. Matsuoka et al. teach or suggest nothing about compounds which may be effective against IBS. Matsuoka et al. would not motivate one of ordinary skill in the art to seek therapeutic agents for IBS.

From Matsuoka et al. one skilled in the art could not have arrived at the idea that the compounds of the present invention would have an action of binding both to the $5\text{-}HT_{1A}$ receptor and to the $5\text{-}HT_3$ receptor, and would have positive effects on IBS. The Examiner's view that "structurally similar compounds would possess similar activity" does not hold, and this rejection should be withdrawn.

2. *Modica et al. and Guccione et al.*

In the last response, Applicants stated, "...the compounds which have a pyrimidine ring at their terminal are weak in $5\text{-}HT_3$ antagonistic activity, and can be said to be unsuitable for the treatment of IBS...."

With regard to the above-quoted statement, the Examiner asserts that: "Examiner finds this use argument unpersuasive if the compounds of the reference are obvious variants of the compounds of the instant claims." The Examiner goes on to suggest, "If Applicant amends the claims as suggested by Examiner, *supra*, then the reference would not read on the rejected claims."

In response to the outstanding Final Rejection, Applicants define Ar in formula (I) of Claim 1 to the moieties which are mentioned in the present specification at pages 8-11. These moieties for Ar are not exactly the same as the twelve moieties suggested by the Examiner, but cover the moieties in compounds which are mentioned in Examples of the present specification,

i.e., the twelve moieties suggested by the Examiner and analogues. It has been either confirmed by pharmacological tests, or would be recognized by one of ordinary skill in the art that the compounds of the present invention, which have these moieties for Ar, have dual activity, i.e., 5-HT_{1A} agonistic activity and 5-HT3 antagonistic activity. The compounds of the present invention are therefore effective against IBS.

Modica et al. and Guccione et al. relate to compounds which act on the central nervous system, and do not mention 5-HT_3. These references neither mention nor suggest that making 5-HT_{1A} agonistic activity and 5-HT_3 antagonistic activity work in cooperation and produces positive effects on IBS. Hence, it would have been impossible to arrive at the present invention from Modica et al. and Guccione et al. Therefore, the compounds of the present invention are unobvious over Modica et al. and Guccione et al., and this rejection should be withdrawn.

No further issues remaining, allowance of this application is respectfully requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact undersigned at the telephone number below.

Respectfully submitted,

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